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(54) **TREATMENT OF MAJOR DEPRESSIVE DISORDER AND SUICIDAL IDEATIONS THROUGH STIMULATION OF HIPPOCAMPAL NEUROGENESIS UTILIZING PLANT-BASED APPROACHES**

(71) Applicant: **THERAPEUTIC SOLUTIONS INTERNATIONAL, INC.**, OCEANSIDE, CA (US)

(72) Inventors: **Thomas Ichim**, Oceanside, CA (US); **Timothy G. Dixon**, Oceanside, CA (US); **James Veltmeyer**, Oceanside, CA (US); **Kalina O'Connor**, Oceanside, CA (US)

(73) Assignee: **THERAPEUTIC SOLUTIONS INTERNATIONAL, INC.**, OCEANSIDE, CA (US)

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(57) **ABSTRACT**

Disclosed are means and methods of treating major depressive disorder and/or other disorders that predispose to suicide by administration of nutraceutical means, wherein said nutraceuticals are administered at a frequency and/or concentration sufficient to induce proliferation of endogenous neural progenitor cells. In one embodiment said nutraceuticals are comprised of green tea extract, and/or *Nigella sativa*, and/or pterostilbene, and/or sulforaphane. In some embodiment's nutraceutical compositions are utilized to overcome treatment resistant of currently used antidepressants.

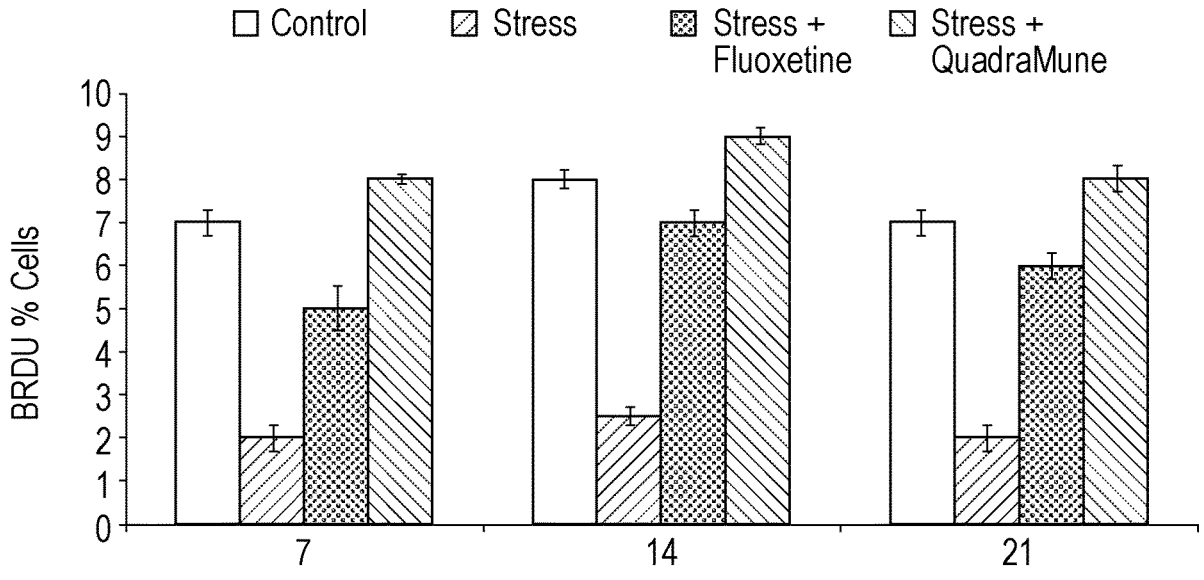
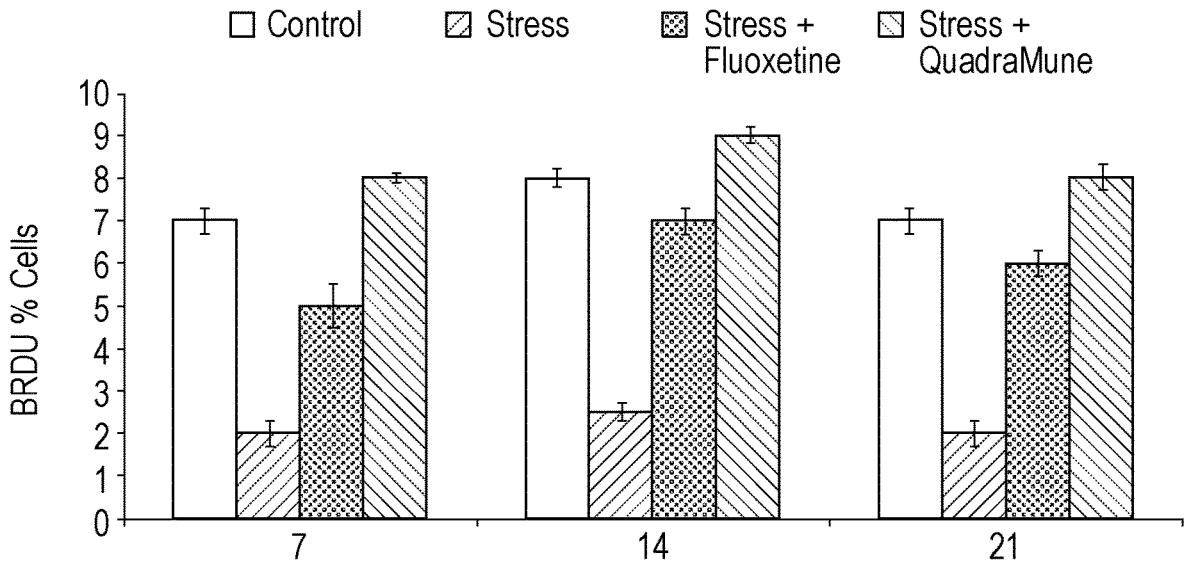


FIG. 1


Control
Stress
Stress + Fluoxetine
Stress + QuadraMune
BRDU % Cells
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TREATMENT OF MAJOR DEPRESSIVE DISORDER AND SUICIDAL IDEATIONS THROUGH STIMULATION OF HIPPOCAMPAL NEUROGENESIS UTILIZING PLANT-BASED APPROACHES

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to U.S. Provisional Application Ser. No. 63/122,862, filed Dec. 8, 2020, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention pertains to the area of psychiatry, more specifically, the invention relates to the utilization of chemicals useful for stimulation of neurogenesis. More specifically the invention relates to the use of neurogenesis for treatment of major depressive disorder.

BACKGROUND OF THE INVENTION

[0003] MDD is a condition associated with depression, lack of interest, anhedonia, fear, feelings of worthlessness, weight loss, insomnia, and inability to maintain concentration. It is believed that MDD has 12-month and lifetime prevalence of 10.4% and 20.6%, respectively [1]. This disease is also often a life-threatening illness with suicide as cause of death for an estimated 10% of patients with severe MDD. Current treatments of MDD include the use of antidepressants, sleep deprivation, electroconvulsive therapy and ketamine.

[0004] An inflammatory basis for MDD has been proposed by several investigators. Initial findings included elevated inflammatory cytokines in the blood of patients. One of the first studies examined data collected from 3024 well-functioning older persons, 70-79 years of age. Depressed mood was defined as a Center for Epidemiologic Studies Depression scale score of 16 or higher. Plasma concentrations of interleukin (IL)-6, tumor necrosis factor (TNF)-alpha, and C-reactive protein (CRP) were measured. Compared with the 2879 nondepressed subjects, the 145 persons with depressed mood had higher median plasma levels of IL-6, TNF-alpha, and CRP. After adjustment for health and demographic variables, depressed mood was especially prevalent among persons who had a high (above median) plasma level for at least two of the inflammatory markers [2]. Numerous other studies have demonstrated upregulation of plasma IL-6 in patients with MDD [3-32].

[0005] Interestingly, pointing to a pathological role of IL-6 are studies in which elevations of this acute phase protein are associated with resistance to psychiatric therapy of MDD. In one study, plasma concentrations of IL-6 was assessed in unmedicated, medically stable patients with MDD (n=98) and varying numbers of adequate antidepressant treatment trials in the current depressive episode as measured by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire. Covariates including age, sex, race, education, body mass index (BMI) and severity of depression were included in statistical models where indicated. The investigators found a significant relationship between number of failed treatment trials and inflammatory markers including IL-6 [33]. In another study demonstrating a role of IL-6 in treatment resistance, twenty-nine patients who suffered from a current major depressive episode diagnosed using DSM-IV-TR criteria and were scheduled to undergo ECT at an academic referral center had levels inflammatory cytokines tested including IL-6 and severity of depressive symptoms (Montgomery-Asberg Depression Rating Scale [MADRS]) were prospectively evaluated before ECT treatment, after the second ECT session, and again at the completion of the index treatment series. The investigators reported that in multivariate analyses, higher levels of IL-6 at baseline, but not other inflammatory markers or clinical variables, were associated with lower end-of-treatment MADRS score [34].

SUMMARY

[0006] Preferred methods include treating major depressive disorder comprising stimulation of adult neurogenesis in a mammal.

[0007] Preferred method include embodiments wherein said adult neurogenesis is stimulated by administration of human chorionic gonadotropin.

[0008] Preferred method include embodiments wherein said adult neurogenesis is stimulated by administration of a nutraceutical composition.

[0009] Preferred method include embodiments wherein said nutraceutical composition contains a mixture containing one or more of: a) pterostilbene; b) sulforaphane; c) green tea extract and; d) nigella sativa.

[0010] Preferred method include embodiments wherein said nutraceutical composition is QuadraMune™.

[0011] v wherein said nutraceutical is administered together with an anti-inflammatory agent.

[0012] Preferred method include embodiments wherein said anti-inflammatory agent is minocycline.

[0013] Preferred method include embodiments wherein the drug chlorpromazine is added said nutraceutical.

[0014] Preferred method include embodiments wherein the drug haloperidol is added said nutraceutical.

[0015] Preferred method include embodiments wherein the drug perphenazine is added said nutraceutical.

[0016] Preferred method include embodiments wherein the drug perphenazine is added said nutraceutical.

[0017] Preferred method include embodiments wherein the drug fluphenazine is added said nutraceutical.

[0018] Preferred method include embodiments wherein the drug clozapine is added said nutraceutical.

[0019] Preferred method include embodiments wherein the drug risperidone is added said nutraceutical.

[0020] Preferred method include embodiments wherein the drug olanzapine is added said nutraceutical.

[0021] Preferred method include embodiments wherein the drug quetiapine is added said nutraceutical.

[0022] Preferred method include embodiments wherein the drug ziprasidone is added said nutraceutical.

[0023] Preferred method include embodiments wherein the drug aripiprazole is added said nutraceutical.

[0024] Preferred method include embodiments wherein the drug paliperidone is added said nutraceutical.

[0025] Preferred method include embodiments wherein said nutraceutical is administered together with an inhibitor of NF-kappa B.

[0026] Preferred method include embodiments wherein said NF-kappa B inhibitor is selected from a group comprising of: NF-kappa B activity is selected from a group comprising of: Calagualine (fern derivative), Conophylline

(*Ervatamia microphylla*), Evodiamine (*Evodiae fructus* component), Geldanamycin, Perrilyl alcohol, Protein-bound polysaccharide from basidiomycetes, Rocaglamides (Aglaia derivatives), 15-deoxy-prostaglandin J(2), Lead, Anandamide, *Artemisia vestita*, Cobrotoxin, Dehydroascorbic acid (Vitamin C), Herbimycin A, Isorhapontigenin, Manumycin A, Pomegranate fruit extract, Tetrandine (plant alkaloid), Thienopyridine, Acetyl-boswellic acids, 1'-Acetoxychavicol acetate (*Languas galanga*), Apigenin (plant flavinoid), Cardamomin, Diosgenin, Furonaphthoquinone, Guggulsterone, Falcarindol, Honokiol, Hypoestoxide, Garcinone B, Kahweol, Kava (*Piper methysticum*) derivatives, mangostin (from *Garcinia mangostana*), N-acetylcysteine, Nitrosylcobalamin (vitamin B12 analog), Piceatannol, Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone), Quercetin, Rosmarinic acid, *Semecarpus anacardiu* extract, Staurosporine, Sulforaphane and phenylisothiocyanate, Theaflavin (black tea component), Tilianin, Tocotrienol, Wedelolactone, Withanolides, Zerumbone, Silibinin, Betulinic acid, Ursolic acid, Monochloramine and glycine chloramine (NH2Cl), Anethole, Baoganning, Black raspberry extracts (cyanidin 3-O-glucoside, cyanidin 3-O-(2(G)-xylosylrutinoside), cyanidin 3-O-rutinoside), Buddlejasaponin IV, Cacospongionolide B, Calagualine, Carbon monoxide, Cardamonin, Cycloepoxydon; 1-hydroxy-2-hydroxymethyl-3-pent-1-enylbenzene, Decursin, Dexanabinol, Digitoxin, Diterpenes, Docosahexaenoic acid, Extensively oxidized low density lipoprotein (ox-LDL), 4-Hydroxynonenal (HNE), Flavopiridol, [6]-gingerol; casparol, *Glossogyne tenuifolia*, Phytic acid (inositol hexakisphosphate), Pomegranate fruit extract, Prostaglandin A1, 20(S)-Protopanaxatriol (ginsenoside metabolite), Rengyolone, Rottlerin, Saikosaponin-d, Saline (low Na+ istonic).

BRIEF DESCRIPTION OF THE DRAWINGS

[0027] FIG. **1** is a bar graph showing the results of stressed mice that were treated with Fluoxetine or QuadraMune™ daily. Assessment of endogenous neurogenesis was performed by administering BRDU and assessment of incorporation by histology.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The invention provides means of stimulating endogenous neurogenesis by administration of nutraceutical compounds alone or in combination with anti-inflammatories and/or other therapeutic agents.

[0029] In one embodiment the invention teaches administration of QuadraMune™ as a means of treating major depressive disorder and/or overcoming resistance to therapeutic effects of antidepressants in treatment of major depressive disorder. In some embodiments probiotics are administered to augment therapeutic efficacy.

[0030] QuadraMune™ or ingredients thereof, alone, or in combination, are disclosed by the current invention for treatment of schizophrenia and/or suicidal ideations. QuadraMune™ is comprised of *Nigella sativa*, Sulforaphane, Pterostilbene, and EGCG.

[0031] Pterostilbene (trans-3,5-dimethoxy-4-hydroxystilbene) is a natural polyphenolic compound, primarily found in fruits, such as blueberries, grapes, and tree wood. It has been demonstrated to possess potent antioxidant and anti-inflammatory properties. It is a dimethylated analog of resveratrol which is found in blueberries [35], and is believed to be one of the active ingredients in ancient Indian Medicine [36]. The pterostilbene molecule is structurally similar to resveratrol, the antioxidant found in red wine that has comparable anti-inflammatory, and anticarcinogenic properties; however, pterostilbene exhibits increased bioavailability due to the presence of two methoxy groups which cause it to exhibit increased lipophilic and oral absorption [37-41]. In animal studies, pterostilbene was shown to have 80% bioavailability compared to 20% for resveratrol making it potentially advantageous as a therapeutic agent [37].

[0032] We have demonstrated the pterostilbene administered in the form of nanostilbene in cancer patients results in increased NK cell activity, as well as interferon gamma production. Additionally, pterostilbene has shown to inhibit inflammatory cytokines associated with ARDS. For example, studies have demonstrated inhibition of interleukin-1 [42], interleukin-6 [43, 44], interleukin-8 [45], and TNF-alpha [46], by pterostilbene.

[0033] It is interesting to note that numerous studies have demonstrated endothelial protective effects of pterostilbene. For example, Zhang et al. investigated the anti-apoptotic effects of pterostilbene in vitro and in vivo in mice. Exposure of human umbilical vein VECs (HUVECs) to oxLDL (200 μg/ml) induced cell shrinkage, chromatin condensation, nuclear fragmentation, and cell apoptosis, but pterostilbene protected against such injuries. In addition, PT injection strongly decreased the number of TUNEL-positive cells in the endothelium of atherosclerotic plaque from apoE(−/−) mice. OxLDL increased reactive oxygen species (ROS) levels, NF-κB activation, p53 accumulation, apoptotic protein levels and caspases-9 and -3 activities and decreased mitochondrial membrane potential (MMP) and cytochrome c release in HUVECs. These alterations were attenuated by pretreatment. Pterostilbene inhibited the expression of lectin-like oxLDL receptor-1 (LOX-1) expression in vitro and in vivo. Cotreatment with PT and siRNA of LOX-1 synergistically reduced oxLDL-induced apoptosis in HUVECs. Overexpression of LOX-1 attenuated the protection by pterostilbene and suppressed the effects of pterostilbene on oxLDL-induced oxidative stress. Pterostilbene may protect HUVECs against oxLDL-induced apoptosis by downregulating LOX-1-mediated activation through a pathway involving oxidative stress, p53, mitochondria, cytochrome c and caspase protease [47]. Endothelial protection by pterostilbene [48, 49], and its analogue resveratrol are well known [50, 51].

[0034] The seeds of Kalonji (*Nigella sativa* Linneaus) are used by the Egyptian public as carminative and flavoring agents in bread and across the Middle East for a variety of food purposes [52]. This black cumin herb goes by many different names. For example, in old Latin it is called as 'Panacea' meaning 'cure all' while in Arabic it is termed as 'Habbah Sawda' or 'Habbat el Baraka' translated as 'Seeds of blessing'. In India it is called as Kalonji while in China it is referred as Hak Jung Chou. The plant belongs to the Ranunculaceae family of flowering plants and genus of about 14 species including *Nigella arvensis, Nigella ciliaris, Nigella damascene, Nigella hispanica, Nigella integrifolia, Nigella nigellastrum, Nigella orientalis* and *Nigella sativa*, respectively. Among these, *Nigella sativa* is the species most exhaustively investigated for therapeutic purposes although other species have also been implicated for therapeutic uses

[53]. Generally therapeutic properties of *Nigella sativa* have including antimicrobial [54-60], antiviral [61-64], antifungal [65, 66], anti-asthmatic/antiairway inflammation [67-81], anti-oxidant [82-86], anti-diabetic [87-97], anti-cancerous [98-113], hepatoprotective [114-127], cardioprotective [128-142], neuroprotective [143-180], renoprotective [181-194], anti-coagulant [195, 196], protects from sepsis [197-199], protects the endothelium [200-204], anti-inflammatory [205-217], and immune stimulatory [197, 218-228].

[0035] First. Taking Kalonji increases the potency of the immune system [229, 230]. Specifically, it has been shown that kalonji activates the natural killer cells of the immune system. Natural killer cells, also called NK cells are the body's first line of protection against viruses. It is well known that patients who have low levels of NK cells are very susceptible to viral infections. Kalonji has been demonstrated to increase NK cell activity. In a study published by Dr. Majdalawieh from the American University of Sharjah, Sharjah, United Arab Emirates [222], it was shown that the aqueous extract of *Nigella sativa* significantly enhances NK cytotoxic activity. According to the authors, this supports the idea that NK cell activation by Kalonji can protect not only against viruses, but may also explain why some people report this herb has activity against cancer. It is known that NK cells kill virus infected cells but also kill cancer cells. There are several publications that show that Kalonji has effects against cancer [98, 100, 109, 231-242].

[0036] Second. Kalonji suppresses viruses from multiplying. If the virus manages to sneak past the immune system and enters the body, studies have shown that Kalonji, and its active ingredients such as thymoquinone, are able to directly stop viruses, such as coronaviruses and others from multiplying. For example, a study published from University of Gaziantep, in Turkey demonstrated that administration of Kalonji extract to cells infected with coronavirus resulted in suppression of coronavirus multiplication and reduction of pathological protein production [243]. Antiviral activity of Kalonji was demonstrated in other studies, for example, for example, viral hepatitis, and others [244].

[0037] Third. Kalonji protects the lungs from pathology. Kalonji was also reported by scholars to possess potent anti-inflammatory effects where its active ingredient thymoquinone suppressed effectively the lipopolysaccharide-induced inflammatory reactions and reduced significantly the concentration of nitric oxide, a marker of inflammation [245]. Moreover, Kalonji has been proven to suppress the pathological processes through blocking the activities of IL-1, IL-6, nuclear factor-κB [246], IL-1β, cyclooxygenase-1, prostaglandin-E2, prostaglandin-D2 [247], cyclocoxygenase-2, and TNF-α [248] that act as potent inflammatory mediators and were reported to play a major role in the pathogenesis of Coronavirus infection.

[0038] Fourth. Kalonji protects against sepsis/too much inflammation. In peer reviewed study from King Saud University, Riyadh, Saudi Arabia, scientists examined two sets of mice (n=12 per group), with parallel control groups, were acutely treated with thymoquinone (ingredient from Kalonji) intraperitoneal injections of 1.0 and 2.0 mg/kg body weight, and were subsequently challenged with endotoxin Gram-negative bacteria (LPS 0111:B4). In another set of experiments, thymoquinone was administered at doses of 0.75 and 1.0 mg/kg/day for three consecutive days prior to sepsis induction with live *Escherichia coli*. Survival of various groups was computed, and renal, hepatic and sepsis markers were quantified. Thymoquinone reduced mortality by 80-90% and improved both renal and hepatic biomarker profiles. The concentrations of IL-la with 0.75 mg/kg thymoquinone dose was 310.8±70.93 and 428.3±71.32 pg/ml in the 1 mg/kg group as opposed to controls (1187.0±278.64 pg/ml; $P<0.05$). Likewise, IL-10 levels decreased significantly with 0.75 mg/kg thymoquinone treatment compared to controls (2885.0±553.98 vs. 5505.2±333.96 pg/ml; $P<0.01$). Mice treated with thymoquinone also exhibited relatively lower levels of TNF-α and IL-2 (P values=0.1817 and 0.0851, respectively). This study gives strength to the potential clinical relevance of thymoquinone in sepsis-related morbidity and mortality reduction and suggests that human studies should be performed [249].

[0039] Sulforaphane [1-isothiocyanato-4-(methylsulfinyl)-butane], an isothiocyanate, is a chemopreventive photochemical which is a potent inducer of phase II enzyme involved in the detoxification of xenobiotics [250]. Sulforaphane is produced from the hydrolysis of glucoraphanin, the most abundant glucosinolate found in broccoli, and also present in other Brassicaceae [251]. Numerous studies have reported prevention of cancer [252-256], as well as cancer inhibitory properties of sulforaphane [257-262]. Importantly, this led to studies which demonstrated anti-inflammatory effects of this compound.

[0040] One of the fundamental features of inflammation is production of TNF-alpha from monocytic lineage cells. Numerous studies have shown that sulforaphane is capable of suppressing this fundamental initiator of inflammation, in part through blocking NF-kappa B translocation. For example, Lin et al. compared the anti-inflammatory effect of sulforaphane on LPS-stimulated inflammation in primary peritoneal macrophages derived from Nrf2 (+/+) and Nrf2 (−/−) mice. Pretreatment with sulforaphane in Nrf2 (+/+) primary peritoneal macrophages potently inhibited LPS-stimulated mRNA expression, protein expression and production of TNF-alpha, IL-1beta, COX-2 and iNOS. HO-1 expression was significantly augmented in LPS-stimulated Nrf2 (+/+) primary peritoneal macrophages by sulforaphane. Interestingly, the anti-inflammatory effect was attenuated in Nrf2 (−/−) primary peritoneal macrophages. We concluded that SFN exerts its anti-inflammatory activity mainly via activation of Nrf2 in mouse peritoneal macrophages [263]. In a similar study, LPS-challenged macrophages were observed for cytokine production with or without sulforaphane pretreatment. Macrophages were pre-incubated for 6 h with a wide range of concentrations of SFN (0 to 50 μM), and then treated with LPS for 24 h. Nitric oxide (NO) concentration and gene expression of different inflammatory mediators, i.e., interleukin (IL)-6, tumor necrosis factor (TNF)-α, and IL-1β, were measured. sulforaphane neither directly reacted with cytokines, nor with NO. To understand the mechanisms, the authors performed analyses of the expression of regulatory enzyme inducible nitic oxide synthase (iNOS), the transcription factor NF-E2-related factor 2 (Nrf2), and its enzyme heme-oxygenase (HO)-1. The results revealed that LPS increased significantly the expression of inflammatory cytokines and concentration of NO in non-treated cells. sulforaphane was able to prevent the expression of NO and cytokines through regulating inflammatory enzyme iNOS and activation of Nrf2/HO-1 signal transduction pathway [264]. These data are significant because studies have shown both TNF-alpha but also interleukin-6 are involved in pathology of COVID-19 [265-275]. The

utilization of sulforaphane as a substitute for anti-IL-6 antibodies would be more economical and potentially without associated toxicity. Other studies have also demonstrated ability of sulforaphane to suppress IL-6 [276-278]. Interestingly, a clinical study was performed in 40 healthy overweight subjects (ClinicalTrials.gov ID NCT 03390855). Treatment phase consisted on the consumption of broccoli sprouts (30 g/day) during 10 weeks and the follow-up phase of 10 weeks of normal diet without consumption of these broccoli sprouts. Anthropometric parameters as body fat mass, body weight, and BMI were determined. Inflammation status was assessed by measuring levels of TNF-α, IL-6, IL-1β and C-reactive protein. IL-6 levels significantly decreased (mean values from 4.76 pg/mL to 2.11 pg/mL with 70 days of broccoli consumption, $p<0.001$) and during control phase the inflammatory levels were maintained at low grade (mean values from 1.20 pg/mL to 2.66 pg/mL, $p<0.001$). C-reactive protein significantly decreased as well [279].

[0041] An additional potential benefit of sulforaphane is its ability to protect lungs against damage. It is known that the major cause of lethality associated with COVID-19 is acute respiratory distress syndrome (ARDS). It was demonstrated that sulforaphane is effective in the endotoxin model of this condition. In one experiments, BALB/c mice were treated with sulforaphane (50 mg/kg) and 3 days later, ARDS was induced by the administration of LPS (5 mg/kg). The results revealed that sulforaphane significantly decreased lactate dehydrogenase (LDH) activity (as shown by LDH assay), the wet-to-dry ratio of the lungs and the serum levels of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) (measured by ELISA), as well as nuclear factor-κB protein expression in mice with LPS-induced ARDS. Moreover, treatment with sulforaphane significantly inhibited prostaglandin E2 (PGE2) production, and cyclooxygenase-2 (COX-2), matrix metalloproteinase-9 (MMP-9) protein expression (as shown by western blot analysis), as well as inducible nitric oxide synthase (iNOS) activity in mice with LPS-induced ALI. Lastly, the researchers reported pre-treatment with sulforaphane activated the nuclear factor-E2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway in the mice with LPS-induced ARDS [280].

[0042] EGCG is similar to sulforaphane in that it has been reported to possess cancer preventative properties. This compound has been shown to be one of the top therapeutic ingredients in green tea. It is known from epidemiologic studies that green tea consumption associates with chemoprotective effects against cancer [281-291]. In addition, similarly to sulforaphane, EGCG has been shown to inhibit inflammatory mediators. The first suggestion of this were studies shown suppression of the pro-inflammatory transcription factor NF-kappa B. In a detailed molecular study, EGCG, a potent antitumor agent with anti-inflammatory and antioxidant properties was shown to inhibit nitric oxide (NO) generation as a marker of activated macrophages. Inhibition of NO production was observed when cells were cotreated with EGCG and LPS. iNOS activity in soluble extracts of lipopolysaccharide-activated macrophages treated with EGCG (5 and 10 microM) for 6-24 hr was significantly lower than that in macrophages without EGCG treatment. Western blot, reverse transcription-polymerase chain reaction, and Northern blot analyses demonstrated that significantly reduced 130-kDa protein and 4.5-kb mRNA levels of iNOS were expressed in lipopolysaccharide-activated macrophages with EGCG compared with those without EGCG. Electrophoretic mobility shift assay indicated that EGCG blocked the activation of nuclear factor-kappaB, a transcription factor necessary for iNOS induction. EGCG also blocked disappearance of inhibitor kappaB from cytosolic fraction. These results suggest that EGCG decreases the activity and protein levels of iNOS by reducing the expression of iNOS mRNA and the reduction could occur through prevention of the binding of nuclear factor-kappaB to the iNOS promoter [292]. Another study supporting ability of EGCG to suppress NF-kappa B examined a model of atherosclerosis in which exposure of macrophage foam cells to TNF-α results in a downregulation of ABCA1 and a decrease in cholesterol efflux to apoA 1, which is attenuated by pretreatment with EGCG. Moreover, rather than activating the Liver X receptor (LXR) pathway, inhibition of the TNF-α-induced nuclear factor-κB (NF-κB) activity is detected with EGCG treatment in cells. In order to inhibit the NF-κB activity, EGCG can promote the dissociation of the nuclear factor E2-related factor 2 (Nrf2)-Kelch-like ECH-associated protein 1 (Keap1) complex; when the released Nrf2 translocates to the nucleus and activates the transcription of genes containing an ARE element inhibition of NF-κB occurs and Keap1 is separated from the complex to directly interact with IKKβ and thus represses NF-κB function [293].

[0043] The anti-inflammatory effects of EGCG can be seen in the ability of this compound to potently inhibit IL-6, the COVID-19 associated cytokine, in a variety of inflammatory settings. For example, in a cardiac infarct model, rats were subjected to myocardial ischemia (30 min) and reperfusion (up to 2 h). Rats were treated with EGCG (10 mg/kg intravenously) or with vehicle at the end of the ischemia period followed by a continuous infusion (EGCG 10 mg/kg/h) during the reperfusion period. In vehicle-treated rats, extensive myocardial injury was associated with tissue neutrophil infiltration as evaluated by myeloperoxidase activity, and elevated levels of plasma creatine phosphokinase. Vehicle-treated rats also demonstrated increased plasma levels of interleukin-6. These events were associated with cytosol degradation of inhibitor kappaB-alpha, activation of IkappaB kinase, phosphorylation of c-Jun, and subsequent activation of nuclear factor-kappaB and activator protein-1 in the infarcted heart. In vivo treatment with EGCG reduced myocardial damage and myeloperoxidase activity. Plasma IL-6 and creatine phosphokinase levels were decreased after EGCG administration. This beneficial effect of EGCG was associated with reduction of nuclear factor-kB and activator protein-1 DNA binding [294]. In an inflammatory model of ulcerative colitis (UC) mice were randomly divided into four groups: Normal control, model (MD), 50 mg/kg/day EGCG treatment and 100 mg/kg/day EGCG treatment. The daily disease activity index (DAI) of the mice was recorded, changes in the organizational structure of the colon were observed and the spleen index (SI) was measured. In addition, levels of interleukin (IL)-6, IL-10, IL-17 and transforming growth factor (TGF)-β1 in the plasma and hypoxia-inducible factor (HIF)-1α and signal transducer and activator of transcription (STAT) 3 protein expression in colon tissues were evaluated. Compared with the MD group, the mice in the two EGCG treatment groups exhibited decreased DAIs and SIs and an attenuation in the colonic tissue erosion. EGCG could reduce the release of IL-6 and

IL-17 and regulate the mouse splenic regulatory T-cell (Treg)/T helper 17 cell (Th17) ratio, while increasing the plasma levels of IL-10 and TGF-β1 and decreasing the HIF-1α and STATS protein expression in the colon. The experiments confirmed that EGCG treated mice with experimental colitis by inhibiting the release of IL-6 and regulating the body Treg/Th17 balance [295].

Example

[0044] BALB/c mice where exposed to random stress 4 times a day by spinning by the tail for 15 seconds. Controls where not stressed. Stressed mice where treated with Prozac or QuadraMune™ daily. Assessment of endogenous neurogenesis was performed by administering BRDU and assessment of incorporation by histology. Augmented neurogenesis was seen in animals which received Prozac, with enhanced neurogenesis in animals taking QuadraMune™. Results are shown in FIG. **1**.

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1. A method of treating major depressive disorder comprising stimulation of adult neurogenesis in a mammal.

2. The method of claim **1**, wherein said adult neurogenesis is stimulated by administration of human chorionic gonadotropin.

3. The method of claim **1**, wherein said adult neurogenesis is stimulated by administration of a nutraceutical composition.

4. The method of claim **3**, wherein said nutraceutical composition contains a mixture containing one or more of: a) pterostilbene; b) sulforaphane; c) green tea extract and; d) *Nigella sativa*.

5. The method of claim **3**, wherein said nutraceutical composition is QuadraMune™.

6. The method of claim **2**, wherein said nutraceutical is administered together with an anti-inflammatory agent.

7. The method of claim **6**, wherein said anti-inflammatory agent is minocycline.

8. The method of claim **2**, wherein the drug chlorpromazine is added said nutraceutical.

9. The method of claim **2**, wherein the drug haloperidol is added said nutraceutical.

10. The method of claim **2**, wherein the drug perphenazine is added said nutraceutical.

11. The method of claim **2**, wherein the drug perphenazine is added said nutraceutical.

12. The method of claim **2**, wherein the drug fluphenazine is added said nutraceutical.

13. The method of claim **2**, wherein the drug clozapine is added said nutraceutical.

14. The method of claim **2**, wherein the drug risperidone is added said nutraceutical.

15. The method of claim **2**, wherein the drug olanzapine is added said nutraceutical.

16. The method of claim **2**, wherein the drug quetiapine is added said nutraceutical.

17. The method of claim **2**, wherein the drug ziprasidone is added said nutraceutical.

18. The method of claim **2**, wherein the drug aripiprazole is added said nutraceutical.

19. The method of claim **2**, wherein the drug paliperidone is added said nutraceutical.

20. The method of claim **2**, wherein said nutraceutical is administered together with an inhibitor of NF-kappa B.

21. The method of claim **20**, wherein said NF-kappa B inhibitor is selected from a group comprising of: NF-kappa B activity is selected from a group comprising of: Calagualine (fern derivative), Conophylline (*Ervatamia microphylla*), Evodiamine (*Evodiae fructus* component), Geldanamycin, Perrilyl alcohol, Protein-bound polysaccharide from basidiomycetes, Rocaglamides (*Aglaia* derivatives), 15-deoxy-prostaglandin J(2), Lead, Anandamide, *Artemisia vestita*, Cobrotoxin, Dehydroascorbic acid (Vitamin C), Herbimycin A, Isorhapontigenin, Manumycin A, Pomegranate fruit extract, Tetrandine (plant alkaloid), Thienopyridine, Acetyl-boswellic acids, 1'-Acetoxychavicol acetate (*Languas galanga*), Apigenin (plant flavinoid), Cardamomin, Diosgenin, Furonaphthoquinone, Guggulsterone, Falcarindol, Honokiol, Hypoestoxide, Garcinone B, Kahweol, Kava (*Piper methysticum*) derivatives, mangostin (from *Garcinia mangostana*), N-acetylcysteine, Nitrosylcobalamin (vitamin B12 analog), Piceatannol, Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone), Quercetin, Rosmarinic acid, *Semecarpus anacardiu* extract, Staurosporine, Sulforaphane and phenylisothiocyanate, Theaflavin (black tea component), Tilianin, Tocotrienol, Wedelolactone, Withanolides, Zerumbone, Silibinin, Betulinic acid, Ursolic acid, Monochloramine and glycine chloramine (NH2C1), Anethole, Baoganning, Black raspberry extracts (cyanidin 3-O-glucoside, cyanidin 3-O-(2(G)-xylosylrutinoside), cyanidin 3-O-rutinoside), Buddlejasaponin IV, Cacospongionolide B, Calagualine, Carbon monoxide, Cardamonin, Cycloepoxydon; 1-hydroxy-2-hydroxymethyl-3-pent-1-enylbenzene,
Decursin, Dexanabinol, Digitoxin, Diterpenes, Docosahexaenoic acid, Extensively oxidized low density lipoprotein (ox-LDL), 4-Hydroxynonenal (HNE), Flavopiridol, [6]-gingerol; casparol, *Glossogyne tenuifolia*, Phytic acid (inositol hexakisphosphate), Pomegranate fruit extract, Prostaglandin A1, 20(S)-Protopanaxatriol (ginsenoside metabolite), Rengyolone, Rottlerin, Saikosaponin-d, Saline (low Na+ istonic).

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